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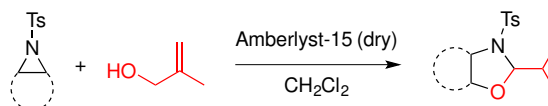
Acid-catalyzed Tandem Process for the One-Pot Synthesis of Oxazolidines

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Dedicated to Prof. Victor Snieckus on the occasion of
his 80th birthday



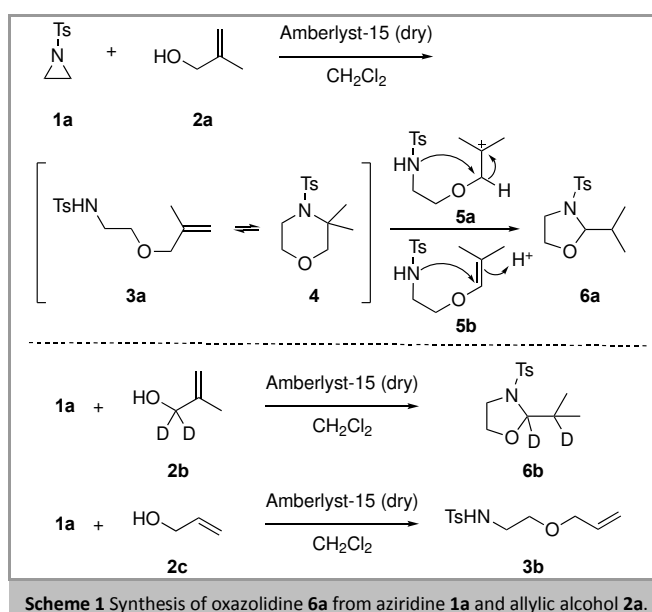
Abstract A simple protocol for the synthesis of oxazolidines from aziridines and allylic alcohols is reported. The solid-supported sulfonic acid catalyst can be easily removed after the reaction by a simple filtration leading to the oxazolidine reaction products in good to excellent yields.

Key words aziridines, cyclization, oxazolidines, rearrangement, ring-opening

Aziridines are important key intermediates in synthesis and many routes for their synthesis have been described. Aziridines can be ring-opened through different processes and allow the facile introduction of C₂N building blocks.¹ The ring opening with oxygen nucleophiles leads to 1,2-aminoalcohol derivatives which are valuable compounds. We describe herein the ring opening of aziridines with 2-methylallyl alcohol followed by a subsequent cyclization leading to oxazolidines.

Oxazolidines are heterocyclic motifs commonly used as protected aminoalcohols, but also embedded in various natural compounds such as quinoxalin,² where the oxazolidine moiety is important for the biological activity. Acid-catalyzed aziridine ring opening reactions using alcohols as nucleophiles have already been reported and proven to be a useful tool for synthesizing aminoalcohol derivatives.³ The use of allylic alcohols for the ring opening reaction provides substrates which have been used for the preparation of six-membered *N*-heterocycles through oxidative palladium-catalyzed cyclizations.⁴ Condensation reactions of aziridines with aldehydes have been reported for the synthesis of oxazolidine derivatives.⁵ We have employed 2-substituted allylic alcohols for the ring opening reaction as this substitution pattern allows the formation of stabilized carbocationic intermediates and, hence, the direct formation of heterocyclic reaction products. Treatment of *N*-tosylaziridines **1** with allylic alcohols **2** in the presence of Amberlyst-15 as a sulfonic acid catalyst provided the oxazolidine derivatives **6** in good yields. The reaction between **1a** and **2a** in the presence of Amberlyst-15 led to

quantitative yield of oxazolidine **6a**. In order to explore the course of the reaction in more detail, the reaction was carried out at lower temperatures (0 °C) and stopped after 1 h. In addition to oxazolidine **6a** (~25%), also the addition product **3** (~25%) and the morpholine derivative **4** (~50%) were detected by ¹H NMR.⁶ If this reaction is continued for another 4 h at 0 °C, only the oxazolidine derivative **6a** is obtained in quantitative yields. Amberlyst-15 does not only provide the reaction conditions for a facile acid-catalyzed aziridine opening which initially leads to compound **3a**, the protonation of the double bond in **3a** leads to a reversible formation of morpholine **4**. Rearrangement of protonated **3a** (or **4**) is accompanied by a hydride transfer as shown in **5a** resulting in the formation of **6a** as the final product.

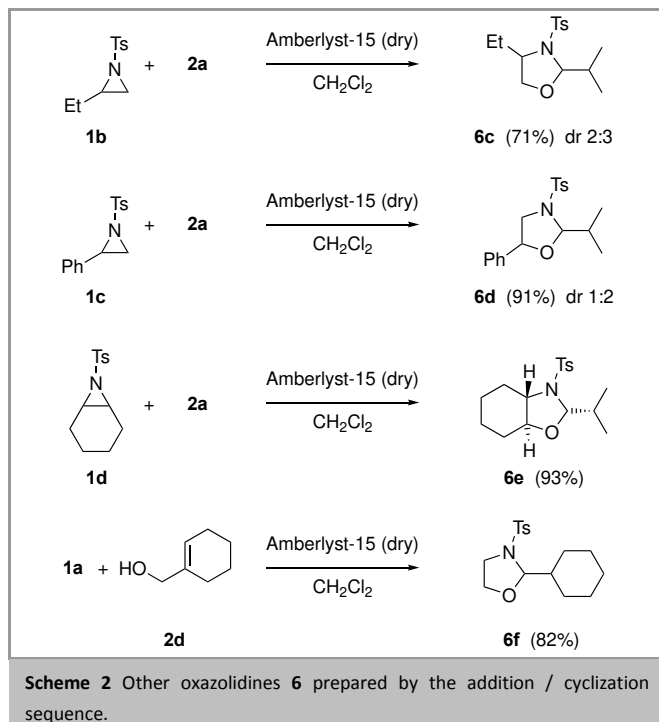


Scheme 1 Synthesis of oxazolidine **6a** from aziridine **1a** and allylic alcohol **2a**.

We recently have reported other cationic rearrangements which were accompanied by hydride transfer.⁷ Alternatively, a double

bond isomerization in **3** would lead to an enol ether **5b** which can also cyclize to oxazolidines as has been shown before.⁸ The use of the deuterated allylic alcohol **2b** led exclusively to the reaction product **6b** indicating that a hydride / deuteride shift as shown in **5a** is operating in this reaction as otherwise only a partially deuterated product would have been obtained. The subsequent reaction to **6a** achieved with the substituted allylic alcohol **2a** and Amberlyst-15 catalyst is remarkable as allylic alcohol **2c** only forms ring-opened addition product **3b** under acid catalysis. Product **3b** is stable and does not further cyclize.^{3a}

Different aziridines can be used in a similar reaction catalyzed by Amberlyst-15. Ethyl-substituted aziridine **1b** is regioselectively ring-opened at the least substituted position providing oxazolidine **6c** in a 2:3 ratio of diastereomers. Phenyl-substituted aziridine **1c** is also regioselectively ring-opened, but exclusively in the benzylic position leading to oxazolidine **6d** in 91% yield. The two diastereomers, obtained in a 1:2 ratio (*trans:cis*), could be separated. The configuration of the *cis*-stereoisomer was confirmed by X-ray analysis.⁹ With the bicyclic aziridine **1d** as starting material, oxazolidine **6e** is formed as a single diastereomer as confirmed by NMR spectroscopy in 93% yield. The relative stereochemistry of the isopropyl substituent was determined by NOESY NMR experiments (see supporting information). Even substituted allylic alcohols such as **2d** can react efficiently with **1a** forming oxazolidine **6f** as product in 82% yield.^{10,11} Amberlyst-15 is a solid-supported sulfonic acid which can be easily removed after the reactions by simple filtration. It is important that dry Amberlyst-15 is used in the process as traces of water can hydrolyze the oxazolidine products to the corresponding aminoalcohols.



In summary, we have developed an operationally very simple protocol for the synthesis of oxazolidines from aziridines and allylic alcohols. The reaction is catalyzed by Amberlyst-15, a solid-supported sulfonic acid, which is removed by filtration after the reaction. The oxazolidine reaction products are obtained in good yields.

Acknowledgment

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Supporting Information

Yes.

Primary Data

No.

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- (10) General procedure: A mixture of *N*-tosylaziridine (**1** mmol), the allylic alcohol (1.1 mmol) in dry dichloromethane (20 mL) was stirred at 0 °C for 10 min, then dry Amberlyst-15 (0.5 g) was added. The mixture was left to warm up to room temperature for 2 hours. The reaction mixture was filtered and washed with dichloromethane (2 x 10 mL). The combined organic layers were concentrated in vacuo and purified by column chromatography on silica gel to afford the oxazolidine as a clear oil.
- (11) Synthesis of **1a** and **1b**: Ye, W.; Leow, D.; Goh, S. L. M.; Tan, C.; Chian, C.; Tan, C. *Tetrahedron Lett.* **2006**, *47*, 1007. Synthesis of **1c**: Ando, T.; Kano, D.; Minakata, S.; Ryu, I.; Komatsu, M. *Tetrahedron* **1998**, *54*, 13485. Synthesis of **1d**: Kano, D.; Minakata, S.; Komatsu, M. *J. Chem. Soc. Perkin Trans. 1* **2001**, 3186. Synthesis of **2b**: Trost, B. M.; King, S. A. *J. Am. Chem. Soc.* **1990**, *112*, 408. Synthesis of **2d**: Hazelden, I. R.; Ma, X.; Langer, T.; Bower, J. F. *Angew. Chem. Int. Ed.* **2016**, *55*, 11198.